

Still's disease in the adult

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Chronic polyarthritis in children, often called Still's disease in Great Britain after G. F. Still, who described 22 cases in 1897, is usually referred to elsewhere (e.g. in the U.S.A.) as 'juvenile rheumatoid arthritis'. This nomenclature prejudices the issue. Is the condition really rheumatoid arthritis, such as occurs in adults, or is it a different disease? This problem has been confronting us at Taplow for more than 20 years: it is complicated by the likelihood that rheumatoid arthritis in adults may consist of a number of different entities, with different manifestations, different courses, and even with different pathogenetic mechanisms, and this suggests the possibility of different treatments. The majority of hospitalized adult patients with rheumatoid arthritis are sero-positive, and this group seems a clear nosological entity, often associated with nodules of a specific histological character. This arthritis is seen also (but rarely) in teenage children. Most patients with chronic polyarthritis in the general population, however, appear to be sero-negative. A few may be included in the latter category who will later be found to develop psoriasis, ulcerative colitis, Crohn's disease, Whipple's disease, ankylosing spondylitis, or other connective tissue disorders. These are all uncommon and, as far as we know, the majority of such sero-negative adult arthritics develop no such stigmata, but remain for many years as cases of 'sero-negative polyarthritis', usually with a milder and less progressive course than patients with sero-positive rheumatoid arthritis. It is to the former group that most of the female relatives of our children with Still's disease appear to belong (Ansell, Lawrence, and Bywaters, 1969).

To find adult patients developing a disease indistinguishable from Still's disease would imply that the latter is a nosological entity *sui generis* and not merely an age-related version of adult polyarthritis. It would also complement the occurrence, at the opposite end of the scale, of children with sero-positive erosive nodular rheumatoid arthritis (as described above) (Bywaters, 1967). This paper sets out to show that the Still's disease syndrome occurs also in adults. In a descriptive study of the rash of Still's disease (or 'juvenile rheumatoid arthritis' as it is often called) published 14 years ago (Isdale and Bywaters, 1956), five adult patients showing the same rash were briefly instanced. The present study con-

cerns fourteen adult patients (including four of the cases previously mentioned by Isdale and Bywaters (1956) with their later development) and particularly the course and manifestations of the disease over a mean observation period of up to 20 years. They have been seen between 1950 (two patients) and 1970 at Taplow and Hammersmith, where we see about 260 and 420 new outpatients per year respectively, including quite a number from outside our own area

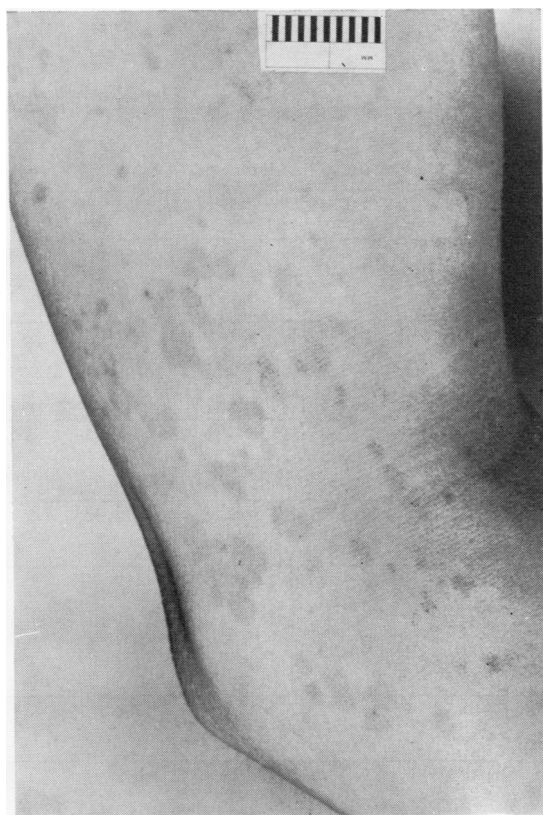


FIG. 1 Case 10. A woman aged 30 years at onset in 1957. She had a 10-year history of intermittent rash—once a year, lasting about a week, worse towards evening, and with trauma and heat; not itchy (scale in mm.). Pain, swelling, and fluid left wrist and right knee for 1 week, subsiding on aspirin. Fever 101°F. Erythrocyte sedimentation rate 58–38 mm./hr; DAT negative; latex test and antinuclear factor negative; rash still present on and off for the next 4 years, but no further joint trouble.

and even from overseas, so that this must be a comparatively rare presentation. Of these fourteen patients, eight were referred locally and six from other more distant hospitals.

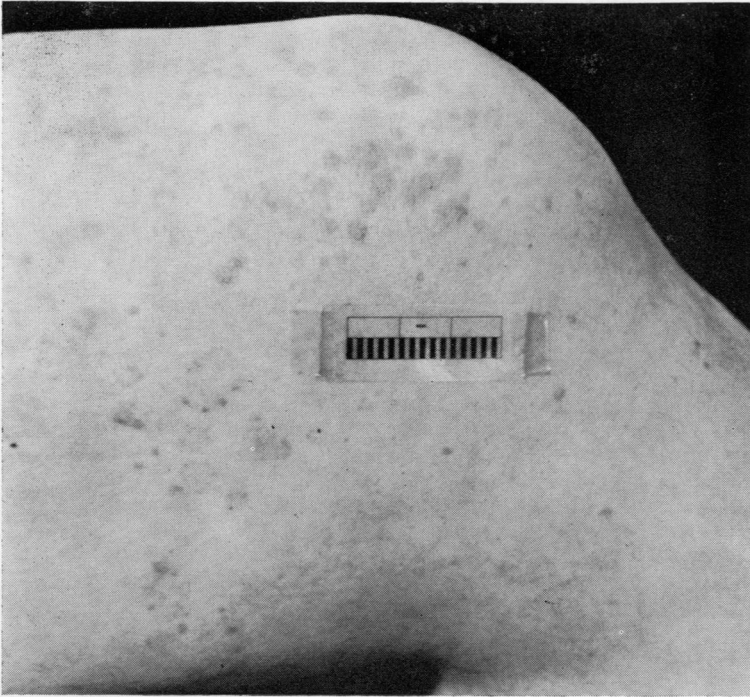
The Table shows that all fourteen patients were female and in the early years of adult life at the time of onset (range 17 to 35 years). Specific features needing discussion are rash, fever, peripheral joint involvement, neck and sacroiliac joint involvement, other clinical features, biopsy findings, serology, and prognosis.

(A) RASH

All fourteen patients showed a typical Still's rash—characterized (Bywaters, 1970) by small macules often with perimacular pallor due to deviation of arteriolar blood from the surrounding skin (Fig. 1); these macules do not spread as in erythema marginatum but disappear during the night and reappear next day in a different area. The macules come up with fever, usually therefore towards 6 p.m. (18.00 hrs.) and may be seen outlining friction lines. Occasionally they may be slightly raised, only very

Table *Clinical particulars of fourteen female patients*

Case no.	Hospital no.	Age at Date of onset		Date first seen by us	Year of follow up	Functional status at follow up	Peripheral joints involved	Radiology			Other	Figs
		(yrs)	onset					Erosions	Neck	Sacroiliac		
1	T.03949	28	1943	Mar. '50	1969	4	Wrists Fingers Shoulders Ankles Knees	+ Ankylosis	Fusion C5-6	0	Splenomegaly Mastoidectomy	Fig. 9
2	T.35577	21	1953	April '55	1969	5	Wrists Fingers Ankles	+ Hands	0	0	Neck limitation Goitre Alopecia Splenomegaly Mastectomy	
3	T.36570	19	1955	July '55	1970	5	Wrists Ankles Knees	Ankylosis carpi	0	Sclerosis	Pericarditis Hairfall No postpartum relapse	Figs 3, 11, 12
4	T.016573	35	1966	Dec. '66	1968	4		+ Carpus	0	Sclerosis	Limitation neck	Fig. 7
5	T.07222	31	1954	Sept. '54	1961	5	Transitory polyarthrititis	0	—	—	Pleural and pericardial effusions 1954 Conjunctivitis	Fig. 2
6	T.89095	31 RF at 16	1964	Nov. '64	1970	3	Wrists Fingers Knees Shoulders Hips	+ +	0	Bilateral sclerosis	Onset followed TB spine Pericarditis Arthroplasty hip	Figs 6, 8, 13
7	HH.204647	31	April '65	May '65 (1 mth after onset)	1970	5	Elbows Wrists Knees Ankles	0	0	0		Fig. 15
8	HH.240163	29 (2 wks before)	1967	Jan. '68	1968	5		0	0	0		
9	T.13940	29	1950	July '50	1965	2	All joints Ankylosis shoulders	+ +	Fusion C12-13	—	Pericarditis and pleural effusions Neck limitation '65 Arthroplasty hips	Figs 5, 10
10	T.46139	30 (1 wk before)	1957	1957	1961	5	Wrists Right knee	0	0	0	Biopsy skin 2776/57	Figs 1, 4
11	HH.307316	17	Jan. '62	Sept. '65	1966	5	Transient joints Right hand and knees	0	—	—		
12	HH.333243	17	June '66	May '67	—	—	Knees, wrists, ankles; swelling and pain over 3 yrs.	0	0	0	Falling hair	Fig. 14
13	HH.300355 Geo.B.96507	33	Oct. '64 Rash	April '65	1969	5	Wrists painful Ankles hot and swollen	—	—	—		
14	HH.284794	34	Mar. '68	Jan. '70	—	—	Tender limited right wrist Fluid TP R.1	0	0 ('70)	0		



rarely itchy. When large they may show a paler centre (Fig. 2), but the margin is never as regular and the diameter never as large as in the erythema marginatum characteristic of rheumatic fever. Usually on the limbs, the rash may also appear on the face and trunk (Fig. 3).

FIG. 2 *Case 5. A woman aged 31 years at onset in 1954. Rash on knee showing central fading (scale in mm.).*

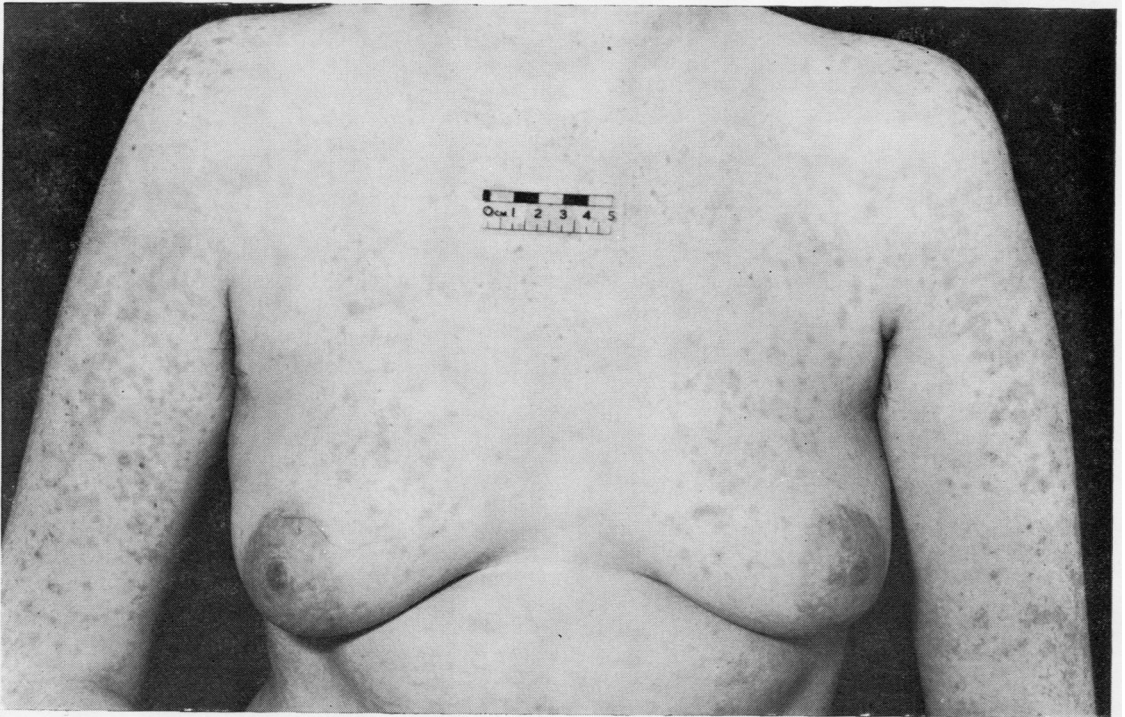


FIG. 3 *Case 3. A woman aged 19 years at onset in 1955. Rash on trunk and limbs intermittent over 8 years (scale in cm.). Onset after sore throat, with fever, pericardial effusion, rash, painful swollen joints, and loss of hair.*

Erythrocyte sedimentation rate 34 mm./hr; blood culture negative. Later developed ankylosis of carpal bones but no disability.

How specific is this rash? It is usually neither itchy nor raised, and it does not spread like the rash of rheumatic fever. Histologically, it showed in cases 1, 2, and 10 (Fig. 4) polymorphs beneath the epidermis quite similar to the juvenile cases. It is quite easily differentiated therefore from the rash of



FIG. 4 Case 10. Biopsy of rash, showing sparse polymorphonuclear leucocyte infiltration of skin. Haematoxylin and eosin. $\times 180$.

rheumatic fever (Isdale and Bywaters, 1956) which shows many perivascular polymorphs and nuclear debris.

We have seen a similar rash (other than in those with *bona fide* Still's disease) in two patients only:

- (1) A child with rash for 6 years since birth and osteochondritis;
- (2) A woman with ulcerative colitis (Case E.B. of Isdale and Bywaters, 1956).

In some stages of chronic urticaria a somewhat similar rash may rarely be seen, and such cases may include Muckle-Well's syndrome. 'Wissler's syndrome' (Wissler, 1944), discussed later, shows a similar rash. A macular rash, usually more persistent, occurs occasionally in the arthritis of sero-positive rheumatoid arthritis, but this is more infiltrated and lasting: on biopsy it shows ischaemic necrosis in the underlying corium due to vasculitis (Bywaters and Scott, 1963).

(B) FEVER

The fever these patients show is often dramatic, especially at the onset of their illness, as in classical Still's disease. It is remittent, as also is classical Still's disease (McMinn and Bywaters, 1959), usually reaching normal levels by morning but rising to 104° – 105° F. (40° C.) in the evening—often for prolonged periods. As in children, this is frequently mistaken for sepsis and treated energetically but in vain with a succession of antibiotics. As also in children, it responds rapidly to an adequate dose of salicylates (Fig. 5, Case 9). All except two (Cases 4 and 8, observed only for a very short time) showed fever of this type.

A few sero-positive adult rheumatoid arthritics show fever for short periods or of low degree, but this is rare and all except one of the adults with

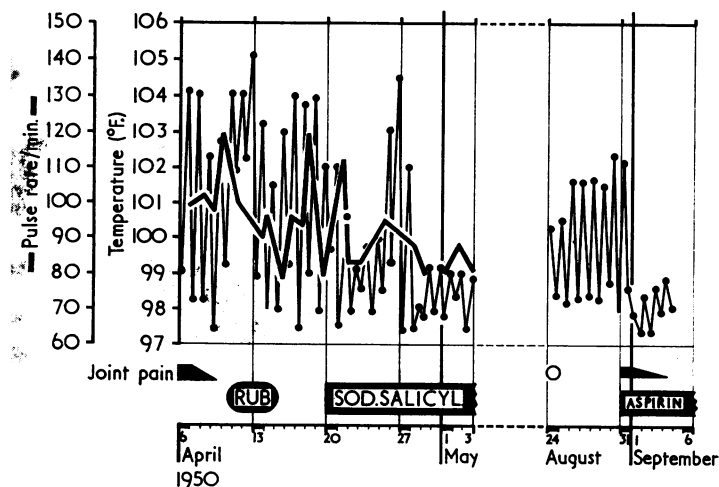


FIG. 5 Case 9. A woman aged 29 years at onset in 1950. Fever at onset responded to salicylates. Many recurrences with fever and later erosions.

marked fever that we have observed are included in the present group.

(C) PERIPHERAL JOINT INVOLVEMENT

This is characteristically fleeting: but once a joint is involved, recurrence is not infrequent. Although it is seldom incapacitating over a long period, the patient may well be off work for a period because of joint disability. The number of joints involved is usually few: as in most types of joint disease, knees, fingers, and wrists are frequently affected, less frequently shoulders and ankles. Hips were involved in only two, Cases 5 and 9. Terminal interphalangeal joints may be selectively affected as in the juvenile disease. The course of joint involvement tends to be mild and in only comparatively few cases were erosions and radiological changes seen (neck and sacroiliac (*q.v.*) and carpus most commonly). Where the carpus was

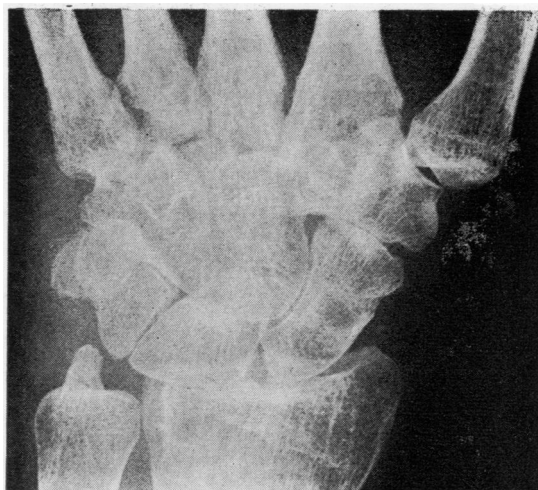


FIG. 7 Case 4. A woman aged 35 at onset in 1966. Radiology of carpus 4 months after onset of polyarthritis in wrists, knees, hands, neck, and shoulders, with rash. Erythrocyte sedimentation rate 69 mm./hr; DAT, latex test, antistreptolysin-O titre, and antinuclear factor negative. Erosions also present in MCP and tarsal joints. When last seen 15 months after onset, she was still febrile.



FIG. 6 Case 6. A woman aged 31 years at onset in 1964. Radiological carpal changes between 1966 and 1968

involved, the ankylosis was curiously limited (Cases 4 and 6: Figs 6 and 7).

Rarely (Cases 5 and 9) were erosions widespread or severe and these were accompanied by the most marked crippling (Fig. 8, overleaf).

(D) NECK

This was of particular interest, since in Still's disease it is the only part of the spine affected, involving 66 per cent. of cases over a 5 to 10-year period according to our figures (Ansell, 1964). Two cases out of eleven showed ankylosis of the apophyseal joints, at C1-2-3 and C5-6 respectively. This is the same type of lesion as that seen in children, but it is usually more extensive in children and may later produce ankylosis of the vertebral bodies as well. Diminution in height of the involved disc with posterior ankylosis was seen in Case 1 (Fig. 9, overleaf) and early calcification or ossification of the involved disc in Case 9 (Fig. 10a, b, c, overleaf) developing between 1950 and 1968. Adult seropositive rheumatoid arthritis not infrequently shows neck involvement, but in contrast to the present cases, hypermobility is usually present often because of multiple disc destruction and subluxations consequent on rheumatoid involvement of the oncovertebral joint spaces and spread therefrom (Ball, 1963). Fusion is very rarely seen in adults' necks (*e.g.* a man aged 35 with onset of classical rheumatoid arthritis, cited by Sharp, 1963). In this respect, therefore, the present cases resemble the juvenile rather than the adult disease.

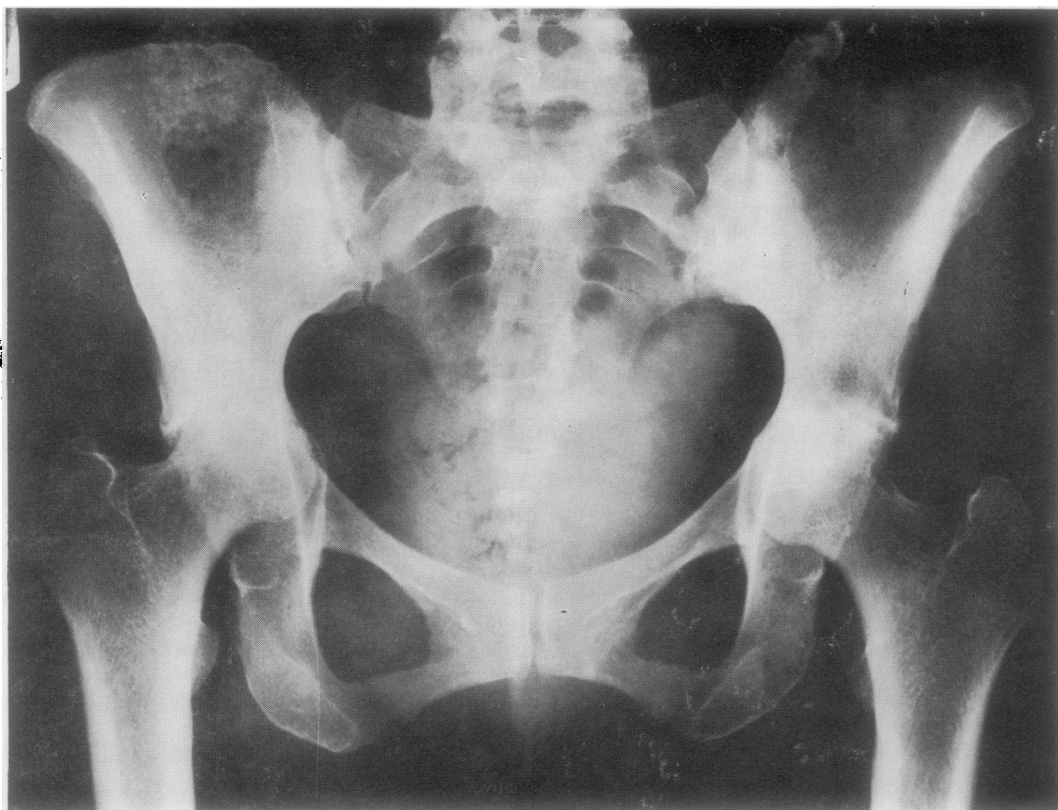


FIG. 8 Case 6. A woman aged 36 in 1969 developed hip lesions 5 years after onset, with fever, rash, polyarthritis. She was seronegative. Sacroiliac sclerosis is probably dependent on hip lesions.

(E) SACROILIAC JOINT

The other radiological lesion encountered in this series was some patchy sclerosis of the sacroiliac joint as in Cases 3 (Fig. 11, overleaf), 4, and 6 (Fig. 8), again comparable to that seen in Still's disease (Carter, 1962) and easily distinguishable from the severe bilateral sacroiliitis of ankylosing spondylitis.

(F) OTHER CLINICAL FEATURES

Hair fall may follow periods of high fever in Still's disease: this was noted in three of the present series (Cases 2, 3, and 12). Transient pericarditis, which occurs in at least 7 per cent. of children with Still's disease (Lietman and Bywaters, 1963), was noted in four cases (3, 5, 6, and 9) and was accompanied by pleural effusions in two (see Table). This occurred at the onset of the disease in Cases 3 (Fig. 12 overleaf), 6, and 9.

Splenomegaly was noted in Cases 1 and 2 only, nodules or iritis in none.

(G) BIOPSY OF SYNOVIAL MEMBRANE

This was performed in four cases. Case 9 showed only normal synovial membrane (wrist) apart from some proliferation of the synovial layer. Case 5

showed oedema and some increase in small blood vessels and fibroblasts with occasional round cells—a very mild inflammation. Case 6 showed synovial cell proliferation and superficial fibrin incorporation with blood vessel proliferation, some polymorphs, and round cell infiltration (Fig. 13, overleaf). Case 12 showed the most active lesion, synovial cell proliferation, an increase in blood vessels, and widespread infiltration with plasma cells and lymphocytes (Fig. 14, overleaf).

(H) WAALER-ROSE AND LATEX TITRES

These were negative in thirteen out of fourteen cases. The exception was Case 7, an otherwise typical example (see Appendix). Waaler-Rose titres in this patient varied from negative (1 : 1; 1 : 4) up to 1 : 32 or 1 : 256, and the latex-fixation test was negative, weak positive, or positive variably in the course of 4 years (Fig. 15, overleaf). It is interesting that this patient was one of the four we have encountered in series of cases of juvenile and adult rheumatoid arthritis in whom the IgA was absent. Antinuclear factor was negative in this case as well as in twelve other cases. Case 14 showed a very weakly positive



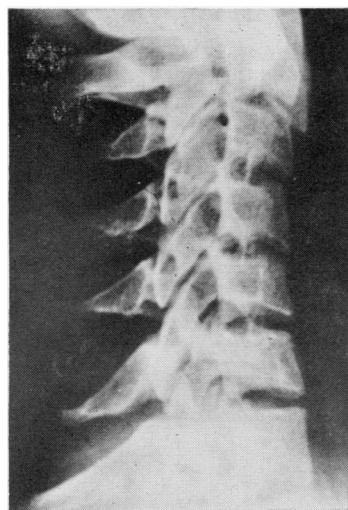
antinuclear factor immunofluorescence at a titre of 1 : 10. No LE-cells were seen.

(i) COURSE OF THE DISEASE

This resembled that of juvenile arthritis rather than that of sero-positive adult rheumatoid arthritis in that it was in most instances benign. Follow-up has varied from 25 years from onset and 18 years from when we first saw the patient to nil in two cases in which we have not been able to follow the patient's course at all. Ten cases have been followed for more than 2 years since onset, and four for over 10 years. In only two has the disease been progressive and crippling (Cases 6 and 9). Case 9 has had to have bilateral hip arthroplasty and leads a life limited to chair and crutches. The majority, however, were leading a full normal life at the time of follow-up—two having married and produced families. In most cases joint involvement was transient, if remittent; in some the most troublesome symptom was the malaise that accompanied the fever and rash: as in the early stages of adult sero-positive rheumatoid arthritis, flitting arthralgia often difficult to localize was common. Cases 4 and 7 have shown minor psychiatric disturbance related to the steroid therapy used.

FIG. 9 Case 1. A woman aged 52 in 1967, showing radiology of neck 24 years after onset (in 1943 at age 28). There is posterior ankylosis of C5-6 with diminution of disc space.

FIG. 10 Case 9. (a) Lateral x-ray of neck in 1950. (b), (c) Lateral x-rays of neck in flexion and extension in 1965, showing apophyseal fusion of C1-2-3 with calcification of disc C2-3.



10(a) 1950



10(b) 1965



10(c) 1965



FIG. 11 Case 3. Radiology of localized sacroiliac sclerosis in 1963 when she was aged 27, i.e. 8 years after onset.

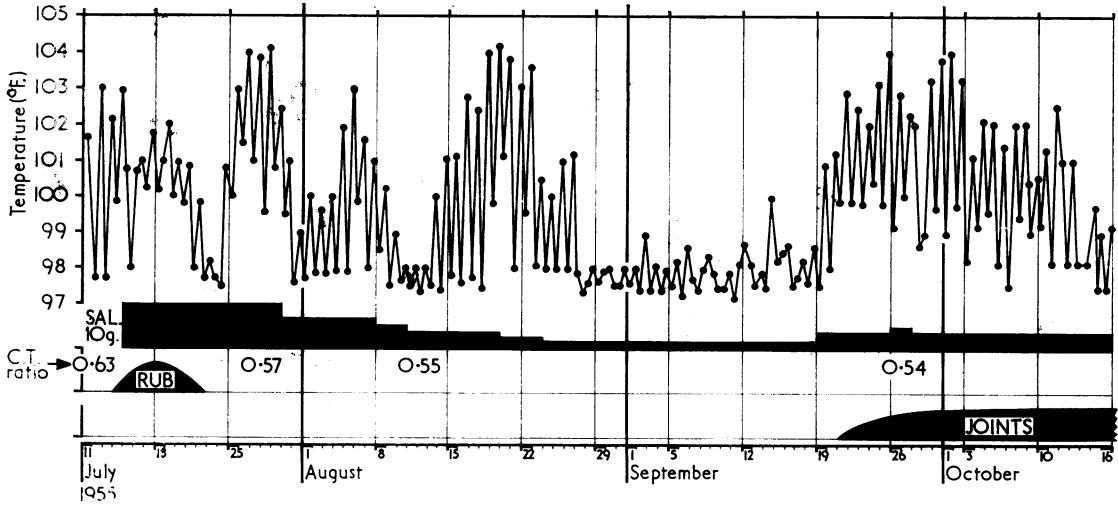


FIG. 12 Case 3. Pericarditis with effusion occurring within 2 weeks of onset.

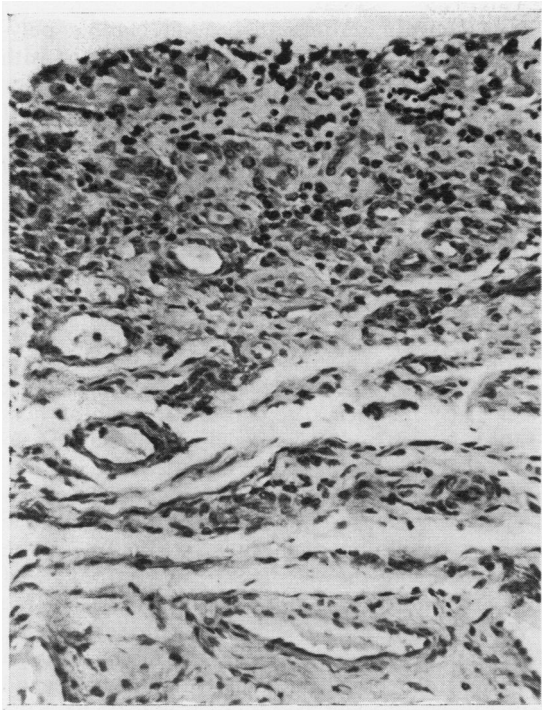


FIG. 13 Case 6. Biopsy of synovial membrane while patient was receiving prednisone 10 mg./day, showing surface hyperplasia and fibrin incorporation, increased vascularity, and lymphocyte accumulation. There are a few plasma cells. Haematoxylin and eosin. $\times 200$.

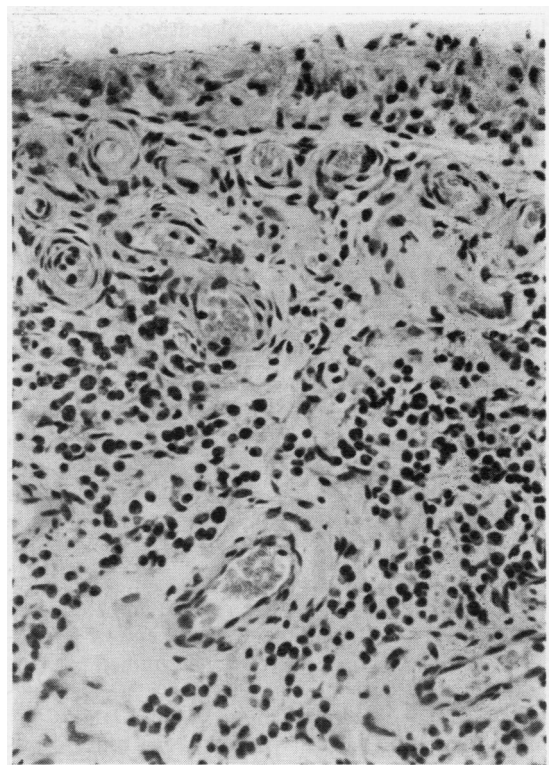


FIG. 14 Case 12. A woman aged 17 at onset in 1966. Biopsy of synovial membrane, showing surface hyperplasia and plasma cell proliferation. Haematoxylin and eosin. $\times 210$.

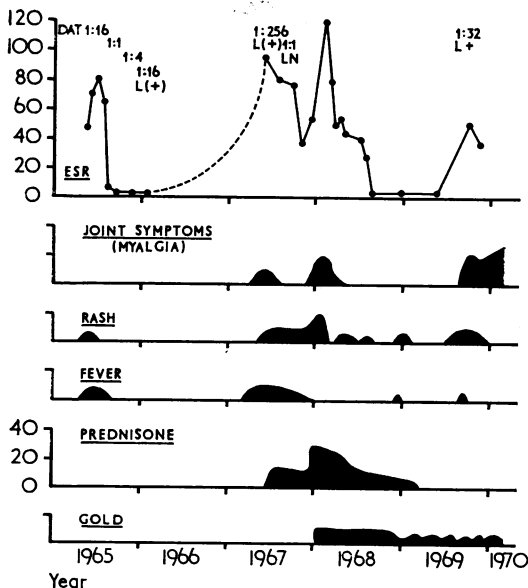


FIG. 15 Case 7. A woman aged 31 at onset in 1965, with a 1-month history of fever, myalgia, and rash. Course over 5 years, showing weaning from prednisone by use of gold. Note Waaler-Rose and latex fluctuations (top line).

Only one patient (Case 9), who had most severe course, has developed a slight trace of protein in the urine (after 15 years of disease) and this has not yet been proved to be due to amyloidosis.

Differential diagnosis

In the first few weeks, care must be taken to differentiate rheumatic fever, rubella, glandular fever, erythema multiforme, allergic reactions with urticaria and hydrarthrosis, and of course such acute treatable infections of the joints accompanied by rash as meningococcal fever.

Discussion

Do these patients have Still's disease or do they fit more easily into the pigeonholes constructed for adult disease, such as sero-negative rheumatoid arthritis, ankylosing spondylitis without spondylitis, ulcerative colitis arthritis without colitis, Crohn's disease arthritis without ileitis, psoriatic arthritis without psoriasis, or other varieties of the Cheshire Cat syndrome? (Bywaters, 1968). We have seen children with ankylosing spondylitis, with Crohn's

disease and arthritis, with ulcerative colitis and arthritis, and with psoriatic arthritis, and we realize that a number of children (as also adults) may have, for instance, psoriatic arthritis for a considerable time before they develop overt psoriasis. However, we must stress that the disease from which the present patients suffer is a sero-negative disease of usually benign prognosis unassociated over a total period of 86 years (mean 8·6; range 1 to 25) with genital, gut, or skin inflammation, and without involvement of the spine other than occasional cervical or sacroiliac lesions—the latter being quite different from those of ankylosing spondylitis. Only one patient had an occasionally positive Waaler-Rose titre.

We have observed most of these patients long enough to know that they are unlikely to develop any of these more severe and more specific complications, and we conclude that, apart from the age at which their disease began, they have juvenile rheumatoid arthritis or Still's disease.

Is there a real difference between 'juvenile type' rheumatoid arthritis or Still's disease and the usual adult type, or is the former just one end of a sero-negative/sero-positive spectrum, determined perhaps by the number and activity of anti-IgG IgM producing cells? This we hope to solve by a study, just begun, of individual cells from synovectomy specimens and their antibody production.

It is not inherently improbable that a disease usually seen in the old should appear occasionally in the young and *vice versa*; we should, however, recognize this abnormal diagnostic problem because, as here, it may have prognostic implications. What is more important is to utilize the age-specific incidence rates as a clue to aetiology, and then, perhaps with good luck, exceptions to the rule might be shown to be subject to some exceptional circumstance which favoured the aetiological hypothesis. Thus, in a country where scurvy is found in children aged 2 to 3 years, scurvy in the elderly on a starvation diet would support the nutritional basis of the disease. So far we have not been successful in producing viable hypotheses, exceptions to which might prove (in the old sense of *testing*) this rule. We have now, however, for the first time recorded a series of cases of what we think to be Still's disease starting in adult life, although we have not been able to show any exceptional circumstances in these patients' histories to account for it. This we hope some day will be done.

Thus, we have now observed on the one hand children with 'adult type' sero-positive arthritis and nodules of the classical rheumatoid arthritis type, and on the other hand adults with juvenile type sero-negative Still's disease. These appear to be different syndromes whether they occur in children or adults. What is more difficult to determine is the difference

if any between sero-negative adult chronic polyarthritis (excluding types specifically associated with psoriasis, colitis, ileitis, Reiter's syndrome, or ankylosing spondylitis) and Still's disease. The fact that a syndrome can be found in adults which matches the children's disease argues for nosological differentiation.

These case histories show beyond doubt that a type of constitutional illness similar to Still's disease in children may occur for the first time in adult life—usually in the third or fourth decade. Like Still's disease it is characterized by high fever, a blotchy transient rash, synovitis, and arthritis, sometimes with erosions and ankylosis—the latter affecting particularly the neck. The pathological appearances of the skin rash and the synovial membrane are also similar. Rheumatoid factor is absent or in low normal titre, as in childhood. Finally, the prognosis is good, function usually being maintained and the symptoms remitting, often for years. These cases are uncommon, but their existence confirms our belief that Still's disease is an entity separate from the ordinary sero-positive rheumatoid arthritis of adults. The latter does, however, occur in children, although it is uncommon and is usually seen in the second rather than in the first decade: such children have the changes seen in adult rheumatoid arthritis—they show rheumatoid factor and the arthritis is widespread and often progressive; only rarely do they show nodules of the adult rheumatoid type and digital vasculitis.

Thus, these two types of disease show some overlap in age incidence as might be expected.

What is the relationship with Wissler's syndrome, or 'subsepsis hyperergica' as he called it in 1943, or 'subsepsis allergica' (Fanconi, 1946)? Quite a number of our juvenile-onset Still's disease patients would fit the description given by Wissler (1944) and we see no reason why the cases he described and those described since under this title should not be ordinary examples of Still's disease or sero-negative juvenile chronic polyarthritis. In our experience there is a complete spectrum between the two poles—on the one hand patients suffering mainly from fever and rash and on the other hand patients suffering mainly from arthritis. There seems to us to be no reason for making a separate category for the former type, although it is true that the patients with rash and fever tend to do better than those with arthritis. There is little evidence for sepsis or subsepsis, for allergy or hyperergy, which was the original speculative categorization.

Most of the cases described as examples of Wissler's syndrome have been seen in children: Wissler (1965), reviewing 25 personal cases and 64 in the literature, could find only a few doubtful cases in adults (Hegglin and Uehlinger, 1964). We have

been able to find in the literature only four descriptions of this syndrome starting in adult life and in some of these the follow-up is poor.

Kalb, Girond, and Félix (1961) described a woman aged 28 years at onset with pericarditis and pleurisy, diagnosed originally as rheumatic fever. In Paris, Riolet (1963) and Duval (1963) apparently described separate adult cases, although we have not been able to consult the original references, and Kemnitz (1968) described a man aged 36 years at onset. Delbarre and Amor (1967) recorded a case in a man aged 38 who was followed for 2 years, but he showed intracellular crystals in synovial fluid (not urate or calcium pyrophosphate). Brette, Thivolet, and Saint-Pierre (1961) also described a possible case. Hegglin and Uehlinger (1964) described very doubtful cases. Even in the recorded juvenile cases it is often not clear whether systemic lupus or rheumatic fever were ruled out. In most of our cases, follow-up has been long enough and study sufficiently detailed to establish that they are indeed similar to those seen in juveniles.

Another possibility seems to us to be the Muckle-Wells syndrome (Muckle and Wells, 1962) due to a hereditary and dominant trait whose phenotype is characterized by an urticarial rash, aguey bouts, nerve deafness, pes cavus, and amyloidosis. Later studies of this syndrome by Kennedy, Rosenthal, and Sneddon (1966), Andersen, Buch, Jensen, and Killmann (1967), and Black (1969) have established that this is essentially one of the familial amyloidoses with onset during adolescence. The picture is not compatible with that described here, although, if any

of our patients had developed amyloidosis (as happened in 6 per cent. of our juvenile cases—Smith, Ansell, and Bywaters 1968), the similarity would be more marked. In view of the resemblance to familial Mediterranean fever, which includes serositis, recurrent arthritis, fever, and rash as well as amyloidosis, it should be stated that all our listed cases were of English stock except Case 13 (Italian).

Finally, it seems probable to us that some of the patients described here would be enumerated in a population survey as cases of 'benign polyarthritis' (Lawrence and Bennett, 1960).

Summary

Fourteen cases are described of an illness starting in adult life resembling Still's disease or the sero-negative chronic polyarthritis of children. Characteristic features are rash, fever, polyarthritis, and raised erythrocyte sedimentation rate. There may also be, as in juvenile cases, pericarditis. Rheumatoid and antinuclear factor are absent from the serum. Ankylosis of the cervical vertebrae may occur. Prognosis is usually good as regards function and joint disease may be minimal. All fourteen patients were female.

My thanks are due to referring physicians (including Dr. Harwood Stevenson (Case 6), Prof. R. E. Tunbridge (Case 12), Dr. Stephen Gold (Case 13) and Dr. Hogarth and Dr. Cairns (Case 14), as well as to my junior colleagues over these 20 years who have provided the records!

Appendix

CASE HISTORIES

Case 6, female

Onset at age 31 (1964) after successful treatment of confirmed TB L2-3 with psoas abscess. Effusion of left knee, pericardial rub, fever, and macular rash. Treated with steroids. There was a previous history of rheumatic fever at age 16.

1965-1969 Continuing fever, rash, and polyarthritis knees, hips, shoulders, and wrists, with erosions. Sacroiliac joints bilateral sclerosis (probably dependent on hip disease). Synovectomy and arthroplasties performed (Figs 6, 8, and 13).

Case 7, female

Onset at age 31 (1965), after abrupt onset 1 month previously of intermittent fever, aching, and rash. Pain and limitation of elbow, wrists, and knees. Blood cultures negative. Fever to 103°F. remittent. Rapidly controlled by aspirin with fall of erythrocyte sedimentation rate from 73 to 5 mm./hr.

Recurrence 1967 First fever and muscle tenderness with rigidity and immovability. 5 weeks later, rash and knee effusions developed. Erythrocyte sedimentation rate 95 mm./hr. Phosphocreatine kinase normal. Electromyograph and electrocardiogram normal. Muscle biopsy mononuclear cell infiltrate. Barium and sigmoidoscopy normal. Treated with prednisone but attacks of rash and fever continued. Under cover of gold injections, steroid therapy was reduced and by 1970 stopped, but the disease was still active, erythrocyte sedimentation rate 67 mm./hr, with slight pain, swelling, and limitation of right wrist but no erosions on x ray. IgA deficiency (< 1 per cent. of normal, Mr. Howard). See Fig. 15.

Case 9, female

Onset at age 29, when first seen at Taplow in 1950 with pain in back and limbs with fever reaching 105°F. for 13 weeks (Fig. 5). Pericardial friction, pleural effusions, macular rash on forearms, and effusions in carpus, knees,

ankles, and elbows. Erythrocyte sedimentation rate 77 mm./hr. Relieved by salicylates.

Recurrence 4 months later with more widespread arthritis and limitation of neck movement. DAT 1 : 4. Cortisone started.

1952 Bilateral hip arthroplasty. Intermittent fever.

1961 Limitation and ankylosis of joints. Erythrocyte sedimentation rate 6 mm./hr, DAT 1 : 1, latex test negative.

Followed to 1965 Heberden's nodes. Getting about on elbow crutches. Maintenance therapy with aspirin and chloroquine. Erythrocyte sedimentation rate 4 mm./hr. Erosions in carpal bones and ankylosis C2-3 (Fig. 10). Good functional state.

Case 12, female

Onset at age 17½ (1966), with fever, rigors, macular rash, lymphadenopathy, and migratory arthralgia of knees, ankles, and wrists. Erythrocyte sedimentation rate 60 mm./hr; Mantoux test and blood cultures negative. Brucella agglutinins and toxoplasmin dye tests normal. Antistreptolysin-O titre < 200. Wassermann reaction and Kahn test normal. LE-cells negative.

Recurrence 6 months later. Proteinuria; antinuclear

factor negative. Alopecia. Treated with prednisone.

1968 Reduction of prednisone but continuance of effusions and rash, high evening fever on 15 mg. prednisone/day. Erythrocyte sedimentation rate 110 mm./hr.

1969 Synovial biopsy compatible with rheumatoid arthritis (Fig. 14). Waaler-Rose, latex, and antinuclear factor repeatedly negative. X rays neck and sacroiliac joints negative.

1970 Improved on gold, aspirin, and prednisone. At work. Small effusion left knee only. Erythrocyte sedimentation rate 4 mm./hr.

Case 4, female

Onset at age 35 (1966) with pain and swelling of knees, wrist, and fingers for 16 days, macular rash forearms and back. Erythrocyte sedimentation rate 69 mm./hr, antistreptolysin-O titre < 200. DAT, latex, and antinuclear factor negative. Treated with prednisone. Erosions developed in carpus, wrists (Fig. 7), and metacarpal and metatarsal joints. Sacroiliac joints showed slight sclerosis but not beyond normal limits.

Last seen 1968 Still febrile and depressed. Treatment with aspirin.

References

- ANDERSEN, V., BUCH, N. H., JENSEN, M. K., AND KILLMANN, S.-A. (1967) *Amer. J. Med.*, **42**, 449 (Deafness, urticaria and amyloidosis. A sporadic case with a chromosomal aberration).
- ANSELL, B. M. (1964) 'The cervical spine in juvenile rheumatoid arthritis', in 'Radiological Aspects of Rheumatoid Arthritis' (Proc. ISRA Symp. May 19-22, 1963), ed. M. E. Carter, p. 233. Int. Congr. Ser. No. 61. Excerpta Medica Foundation, Amsterdam.
- , BYWATERS, E. G. L., AND LAWRENCE, J. S. (1969) 'Familial aggregation and twin studies in Still's disease', in 'Population Studies and Genetics', ed. J. Rotstein (*Rheumatology*, **2**, 37). Karger, Basel.
- BALL, J. (1963) 'The articular pathology of rheumatoid arthritis', in 'Radiological Aspects of Rheumatoid Arthritis', p. 25 (see above).
- BLACK, J. T. (1969) *Ann. intern. Med.*, **70**, 989 (Amyloidosis, deafness, urticaria and limb pains. A hereditary syndrome).
- BRETTE, R., THIVOLET, J., AND SAINT-PIERRE, A. (1961) *Lyon Méd.*, **205**, 297 (Un cas possible de syndrome de Wissler-Fanconi chez l'adulte).
- BYWATERS, E. G. L. (1967) *Ann. rheum. Dis.*, **26**, 185 (Categorization in medicine: a survey of Still's disease).
- (1971) In 'Dermatology in General Medicine', ed. T. B. Fitzpatrick. McGraw-Hill, New York. (In press).
- AND SCOTT, J. T. (1963) *J. chron. Dis.*, **16**, 905 (The natural history of vascular lesions in rheumatoid arthritis).
- CARTER, M. E. (1962) *Ann. rheum. Dis.*, **21**, 105 (Sacro-iliitis in Still's disease).
- DELBARRE, F., AND AMOR, B. (1967) 'Le syndrome de Wissler-Fanconi', in 'Monographies Internationales de Rhumatologie', no. 2, ed. F. Delbarre and A. Peylan, p. 213.
- DUVAL, J. (1963) Thèse de Paris (cited by Delbarre and Amor, 1967). (Three cases of Wissler-Fanconi syndrome).
- FANCONI, G. (1946) *Helv. paediat. Acta*, **1**, 532 (Über einen Fall von Supsepsis allergica Wissler).
- HEGGLIN, R., AND UEHLINGER, E. (1964) *Schweiz. med. Wschr.*, **94**, 682 (Klinisch-pathologisch-anatomische Fälle 6, 7, 8: Febris periodica hyperergica).
- ISDALE, I. C., AND BYWATERS, E. G. L. (1956) *Quart J. Med.*, **25**, 377 (The rash of rheumatoid arthritis and Still's disease).
- KALB, J. C., GIROUD, M., AND FÉLIX, H. (1961) *Poumon Coeur*, **17**, 465 (Maladie de Wissler-Fanconi chez l'adulte).
- KEMNITZ, H. (1968) *Beitr. Rheum.*, **13**, 204 (Subsepsis allergica Wissler im Erwachsenenalter).
- KENNEDY, D. D., ROSENTHAL, F. D., AND SNEDDON, I. B. (1966) *Brit. med. J.*, **1**, 31 (Amyloidosis presenting as urticaria).
- LAWRENCE, J. S. (1969) 'The epidemiology and genetics of rheumatoid arthritis', in 'Population Studies and Genetics', p. 1 (see above).
- AND BENNETT, P. H. (1960) *Ann. rheum. Dis.*, **19**, 20 (Benign polyarthritis).
- LIETMAN, P. S., AND BYWATERS, E. G. L. (1963) *Pediatrics*, **32**, 855 (Pericarditis in juvenile rheumatoid arthritis).

- McMINN, F. J., AND BYWATERS, E. G. L. (1959) *Ann. rheum. Dis.*, **18**, 293 (Differences between the fever of Still's disease and that of rheumatic fever).
- MUCKLE, T. J., AND WELLS, M. (1962) *Quart. J. Med.*, **31**, 235 (Urticaria, deafness and amyloidosis: a new heredo-familial syndrome).
- RIOLET, J. (1936) *Thèse de Paris* (Abstr. *Rev. Rhum.* (1964) **31**, 368) (Syndrome de Wissler-Fanconi . . . chez un adulte).
- SHARP, J. (1963) 'Cervical spine', in 'Radiological Aspects of Rheumatoid Arthritis', p. 219 (see above).
- SMITH, M. E., ANSELL, B. M., AND BYWATERS, E. G. L. (1968) *Ann. rheum. Dis.*, **27**, 137 (Mortality and prognosis related to the amyloidosis of Still's disease).
- STILL, G. F. (1897) *Med-chir. Trans.*, **80**, 47 (On a form of chronic joint disease in children).
- WISSLER, H. (1944) *Mschr. Kinderheilk.*, **94**, 1 (Über eine besondere Form sepsisähnlicher Krankheiten (subsepsis hyperergica)).
- (1965) *Ergebn. inn. Med. Kinderheilk.*, n.s. **23**, 202 (Subsepsis allergica).